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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Rod Hewick, et al.

Serial No. : 07/800,364 Art Unit: 1814

Filed : November 26, 1991 Examiner: K. Furman

Title : BONE AND CARTILAGE INDUCTIVE PROTEINS

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AG 10/27

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BY: Ellen J. Kapinos

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

STATEMENT PURSUANT TO 37 CFR 1.825(a)

Pursuant to Part III of the Final Office Action dated April 7, 1994 received from the Patent and Trademark Office stating that the "Sequence Listing" does not comply with the requirements of §§1.821 through 1.825, a substitute and amended copy of the computer readable form of the Sequence listing which was duly submitted with the application as filed, is provided herewith.

Please substitute this amended Sequence Listing for the originally-filed Sequence Listing. The Sequence Listing and enclosed diskette now contain SEQ ID NOS:1-15.

This affirms that to the best of my knowledge and belief, these amendments present no substantive changes to the Sequence Listing and the computer readable copy of said Sequence Listing as originally filed. No new matter has been added.

Respectfully submitted,

October 4, 1994
Date

Ellen J. Kapinos
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 and Trademarks
 Washington, D.C. 20231

STATEMENT PURSUANT TO 37 CFR 1.825(b)

Sir:

A substitute and amended copy of the computer readable form of the Sequence Listing which was
 duly submitted with the application, as filed, is provided herewith. This affirms that to the best of my
 knowledge and belief, the content of the substitute Sequence Listing and the computer readable copy of
 said Sequence Listing provided herewith are the same.

Respectfully submitted,

October 4, 1994
 Date

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APPENDIX A

6. An isolated DNA sequence encoding a BMP-8 protein comprising the following sequences

a)

GTG CAC CTG CTG AAG CCG CAC GCG GTC CCC AAG GCG TGC TGC GCG CCC
ACC AAG CTG AGC GCC ACT TCC GTG CTC TAC TAC GAC AGC AGC AAC AAC
GTC ATC CTG CGC AAG CAC CGC AAC ATG GTG GTC CGC GCC TGC GGC TGC
CAC (SEQ ID NO: 7);

b)

GAC TGG GTC ATC GCC CCC CAA GGC TAC TCA GCC TAT TAC TGT GAA GGG
GAG TGC TCC TTC CCG CTG GAC TCC TGC ATG AAC GCC ACC AAC CAC GCC
ATC CTG CAG TCC CTG (SEQ ID NO: 9); and

c)

GAC GTC CAC GGC TCC CAC GGC CGG CAG GTG
TGC CGT CGG CAC GAG CTG AGC TTC CAG GAC CTG GGC TGG CTG (SEQ ID
NO: 11)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

7. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO:13 from nucleotide #8 to #850.

8. An isolated DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO: 13 from nucleotide #434 through #850.

9. An isolated DNA comprising the nucleotide sequence of ATCC #75010 encoding BMP-8.

13. A host cell transformed with a DNA of claim 6.

14. A host cell transformed with the DNA of claim 7.

15. A host cell transformed with the DNA of claim 8.

16. A host cell transformed with the DNA of claim 9.

17. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 6 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

18. A method comprising the steps of

- (a) culturing a cell transformed with a vector comprising

a DNA sequence of claim 9 in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence characterized by the ability to induce the formation of cartilage and/or bone.

19. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence comprising nucleotide #8 through #850 of SEQ ID NO:13 said DNA sequence in operative association with an expression control sequence therefore; and

(b) recovering, isolating, and purifying from said culture medium a protein characterized by an amino acid sequence comprising amino acid #4 to #142 of (SEQ ID NO:14).

26. A method comprising the steps of:

(a) culturing a cell transformed with a vector comprising a DNA sequence of claim 7 said DNA sequence in operative association with an expression control sequence therefor; and

(b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

27. A method comprising the steps of:

- (a) culturing a cell transformed with a vector comprising a DNA sequence of claim 8 said DNA sequence in operative association with an expression control sequence therefor; and
- (b) recovering, isolating and purifying from said culture medium a protein encoded by said DNA sequence.

28. An isolated DNA sequence encoding a BMP-8 protein comprising the following amino acid sequences:

- a) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:1);
- b) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and
- c) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3)

said BMP-8 protein characterized by the ability to induce the formation of cartilage and/or bone.

29. The DNA of claim 6 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a

molecular weight of 14,000-20,000 daltons.

30. The DNA of claim 28 wherein said protein has a molecular weight of 28,000-38,000 daltons and under reducing conditions a molecular weight of 14,000-20,000 daltons.

31. A vector comprising the DNA of claim 28.

32. A DNA sequence which hybridizes under stringent conditions to the sequence of claim 28 and encodes a BMP-8 protein.

33. A method comprising

a) culturing a cell transformed with a vector comprising a DNA of claim 28 in operative association with an expression control sequence therefor; and

b) recovering, isolating and purifying from said culture medium a BMP-8 characterized by the following sequences

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO: 1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

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iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

35. An isolated DNA comprising the nucleotide sequence of ATCC
#75011 encoding BMP-8.